European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2011; 15: 25-34

Hip viscosupplementation under ultra-sound guidance riduces NSAID consumption in symptomatic hip osteoarthritis patients in a long follow-up. Data from italian registry

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Abstract. – *Introduction:* **Non-steroidal anti-inflammatory drugs (NSAIDs) consumption is strictly related to a high gastrointestinal and cardiovascular mortality and morbidity rate. Osteoarthritis Research Society International (OARSI) recommendations in patients with symptomatic hip or knee OA stated that NSAIDs should be used at the lowest effective dose but their long-term use should be avoided if possible. OARSI guidelines for the treatment of the hip OA include the use of viscosupplementation, which aims to restore physiological and rheological features of the synovial fluid.**

Objective: **Aim of this multicentric, open and retrospective study is to investigate if NSAID consumption may be reduced by the use of ultrasound-guided intra-articular injection of several hyaluronic acid (HA) products in hip joint administered in patients affected by symptomatic hip OA.**

Materials and Methods: **Patients affected by mono or bilateral symptomatic hip OA according to American Rheumatology Association (ARA) criteria, radiological OA graded II-IV (Kellgren and Lawrence) entered the study and were administered with ultrasound-guided intra-articular injection of hyaluronic acid products. As a primary endpoint, consumption of NSAIDs was evaluated by recording the number of days a month (range 0-30) the patient had used NSAID during the previous month, reported at each visit during the 24 months follow-up period. Secondary endpoints included further analysis for subgroups of patients categorized for Lequesne index score, Kellgren-Lawrence score, pain visual analogue scale (VAS) score, ultrasound pattern, age, hyaluronic acid used.**

Results: **2343 patients entered the study. Regarding primary endpoint, the consumption of NSAIDs was reduced of 48.2% at the third month when compared with baseline values. This sparing effect increased at 12th and 24th month with a reduction respectively of 50% and 61% in comparison to baseline values. These differences were statistically significant.**

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Conclusions: **These data point out that intra-articular hyaluronan preparations provide OA pain relief and reduce NSAIDs consumption in a large cohort of patients for a long period of follow-up. Multiple courses of viscosupplementation (vs) are required to maintain low dose of NSAID consumption over time. NSAIDs consumption is strictly related to an high gastrointestinal and cardiovascular mortality and morbidity rate, instead HA intra-articular treatment is well tolerated and is associated with a low incidence of adverse effects. For these reasons further studies evaluating cost-effectiveness and cost-utility of VS in the management of hip OA are required.**

Key Words:

Hip, Osteoarthritis, NSAID, Ultrasound, Intra-articular injection, Hyaluronic acid.

Introduction

The prevalence of hip osteoarthritis (OA) is about 3% to 6% in the Caucasian population and has not changed in the past four decades[1]. In OA hip involvement is the most frequent after knee joint.

Treatment designed for symptomatic hip OA tries to reduce pain, maintain and/or improve joint mobility, and limit disabilities. For this purpose physicians use nonpharmacologic modalities, including patient education and physical and occupational therapy as well as pharmacologic agents, both analgesics and non-steroidal anti-inflammatory drugs (NSAIDs)[2]. For many patients with OA the relief of mild-to-moderate joint pain afforded by the simple analgesic acetaminophen is comparable with that achievable with a NSAID[3].

Wolfe et al[4], in a meta-analysis (MA) of trials comparing simple analgesics with NSAIDs in patients with knee OA noted that NSAID-treated patients had significantly greater improvement in both pain at rest and pain on motion. In another study[5] diclofenac was statistically superior to acetaminophen for both pain and function measured with several validated outcome measures. Evidence that NSAIDs are superior to acetaminophen for pain relief in patients with lower limb joint OA is available from another 2004 MA of randomised controlled trials (RCTs). The clinical response rate was higher (RR ¼ 1.24, 95% CI 1.08, 1.41) and the number of patients preferring NSAIDs to acetaminophen was considerably greater (RR ¼ 2.46, 95% CI 1.51, 4.12)[6].

NSAIDs drugs are very effective analgesics, but along with the benefits they can cause some harm as well, including gastrointestinal (GI) bleeding[7], renal failure[8] and congestive heart failure[9]. The incidence of serious vascular events was 1% per annum in patients treated with COX-2 selective agents compared with 0.9% in those on traditional NSAIDs. A recent Cochrane systematic review of short-term RCTs[10] shows that the risk of NSAIDs caused serious GI complications, such as peptic ulcers, perforations and bleeds increasing with age, concurrent use of other medications, and with the duration of therapy[11]. These adverse effects can be severe and may result in death[12].

Recently OARSI recommandations[13] in patients with symptomatic hip or knee OA stated that non-steroidal anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with coprescription of a proton pump inhibitor (PPI) or misoprostol for gastroprotection may be considered. However, NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with cardiovascular (CV) risk factors.

OARSI guidelines for the treatment of the HIP OA include the use of viscosupplementation (VS), which aims to restore physiological and rheological features of the synovial fluid. Viscosupplementation is provided by the intra-articular injection of hyaluronic acid (HA) products, a naturally occurring polymer present in the synovial fluid, or its derivatives.

Even though intra-articular hip injection may be performed "blindly", nevertheless failure rate is significant[14]. For such reasons, it has been suggested to perform intra-articular injection of the hip under radiological or ultrasound guidance. This is one of the limiting factors for this practice, consequently few data exist in literature about the viscosupplementation for the treatment of hip OA[15]. Other Authors[16,17], would rather use ultrasound guidance. Even if there are some data about efficacy of viscosupplementation of hip, confirming a therapeutic effect similar to that achieved in knee OA, data about cost effectiveness are much more scarce. In all our researches we have made use of NSAIDs consumption rate as a pharmacoeconomical efficacy and validity parameter showing its progressive and time sustained percentage reduction. In order to confirm

these preliminary data we perform the present study to evaluate reduction of NSAID intake in a large cohort of patients affected by hip OA after intra-articular injection of Hialuronans under ultrasound monitoring, for a long period of followup to suggest further study of cost-effectiveness and cost-utility.

Subjects and Methods

Study Design

This is a multicentric, open and retrospective study regarding NSAID consumption after US-guided intra-articular injection of several hyaluronic acid products in hip joint administered in patients affected by symptomatic hip osteoarthritis. The Ethical Committee of S. Pietro Hospital, Rome, Italy gave approval.

Patients Selection

Inclusion Criteria: Patients studied had mono or bilateral symptomatic hip OA according to American Rheumatology Association (ARA) criteria[18], radiological OA graded II-IV (Kellgren and Lawrence[19] assessed within the three previous months. Exclusions included use of anticoagulant therapy (to avoid the possibility of intra-articular or pericapsular haemorrhages) and absence of articular space at radiological or ultrasound assessment since a recent review of 80 patients with symptomatic knee OA treated with hyaluronic acid, revealed that patients with a complete collapse of joint space or bone loss showed a poor clinical response.

Treatment

Injections were given according to symptoms and clinical judgment; namely one or two injections every six months according to patients' clinical condition. One 2 ml ampule was used with high molecular weight HA, e.g. Synvisc and Euflexxa; two 2 ml ampule (a total of 4 ml) with low or medium molecular weight HA, e.g. Hyalgan, Hyalubrix 30 mg/ml, Jointex, and Ortoial.

Injection Technique

Patients underwent hip injection under control of ultrasound as described previously[17]. Briefly, patient was examined supine with the hip in internal-rotation of 15-20°. A 7 MHz linear or 3.5 MHz convex transducer (Star 256, Hitachi-Esaote, Genoa Italy) was used with a sterile biopsy guide attached. Hip joint was scanned by means of an anterior parasagittal approach.

NSAIDs Consumption Evaluation

Consumption of NSAIDs was evaluated by recording the number of days a month (range 0-30) the patient had used NSAID during the previous month, reported at each visit during the follow-up period. Each patient was followed-up every three months after the first intra-articular injection.

Primary Endpoint

NSAIDs consumption reduction during 24 months observation time.

Secondary Endpoint

Consumption of NSAIDs analized by subgroups related to:

1. Three HA more used (Synvisc, Hyalubrix, Jointex);
2. Radiological grading of osteoarthritis according to Kellegren-Lawrence classification by grade II-III-IV;
3. Ultrasound grading according to our scoring previously described, arranged in two classes: group A composed by normal femoral head profile (score 1); group B composed by flattening of the femoral head profile, reduction of the angle of the femoral head-neck junction profile caused by initial deformity of the femoral head and irregular femoral head profile with osteophytes and/or bone erosions (respectively score 2-3-4);
4. Patients' age arranged in the following classes: <50, 51-70, >71;
5. Algofunctional Lequesne[21] score at the basal evaluation arranged by low, medium and high grade (<6, 6-10, >10);
6. Patients' pain VAS score arranged in classes 0-4, 5-8, 9-10.

Statistics

The average NSAIDs consumption obtained for each control visit (3, 6, 9, 12, 15, 18, 21, and 24 months) has been compared with the others and with the baseline value by parametric t-test or Wilcoxon's test.

Moreover NSAIDs consumption has been evaluated in different covariance subsets for baseline and for each control visit by indipendent t-test or Mann Whitney's U test. The covariances

considered are: age (categorized as <50, 50-70, >70), pain VAS (categorized as <5, 5-8, >8 on a 0-10 scale), the Lequesne Index (<6, 6-10, >10), the ultrasound score (0, 1, 2, 3), the Kellgren-Lawrence Index[1-4] and the administered drug[1,3,5].

Results

We enrolled 2343 patients affected by mono (2140 pts) or bilateral (203 pts) OA of the hip according to the ARA criteria. Patients' demographics are shown in Table I.

Primary Endpoint

We determined the average NSAIDs consumption for each quarter from baseline to two years follow up in 2343 patients.

Globally patients had taken NSAIDs for a mean of 8.2 days a month before injection and 4.1 and 3.2 days a month respectively 12 and 24 months after treatment. The NSAID consumption trend by each quarter is shown in Figure 1. There is a significant statistical difference in NSAIDs consumption between baseline and each time point after the first injection for a followup of 24 months, while there is no significant statistical difference in NSAIDs consumption between every previous quarter.

The consumption of NSAIDs is reduced of 48.2% at the third month. This sparing effect has increased at the 12th and 24th month with a reduction respectively of 50 and 61% in comparison to the month before the first injection in patients persisting under intra-articualr tratment. These differences were statistically significant.

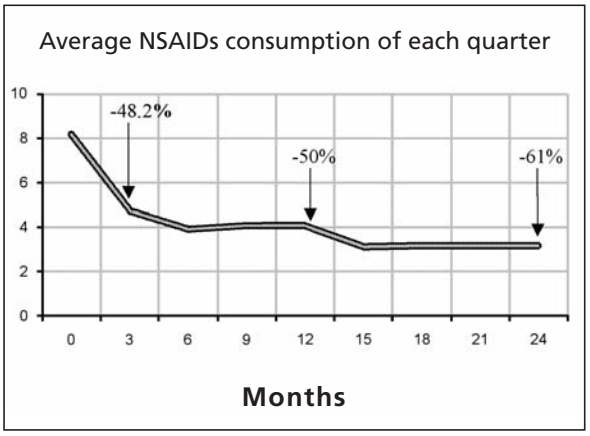


Figure 1. NSAIDs consumption trend of each quarter.

Secondary endpoint: To detect correlations between clinical features and NSAIDs consumption reduction along time we performed an analysis based upon different patients' subsets in relation with age, Lequesne index, VAS pain scale, ultrasound score, K/L radiological index and HA injected.

Results of Subgroups

Patients' Age

At baseline patients were divided in different age groups: <50 (424 patients), 51-70 (1199 patients) and >71 (641 patients). In the three age-groups there is a statistically significant difference in the average NSAIDs consumption among the most distant ages (<50 vs >70 years) (Figure 2A). After 12 and 24 months class 1 patients showed a reduction of 60% and 65%, while those in class 2 of 49.4% and 52.3% and those in class 3 of 47.1% and 70.6%.

Algofunctional Lequesne Score

Regarding Lequesne score, 531 patients fell within 00-05 group (class 1) and respectively 983 within 06-10 (class 2) and 796 within >11 (class 3). NSAIDs consumption in the three groups is statistically different when comparing baseline value with values obtained at each control visit and in each class (<6 vs 6-10 vs >10) (Figure 2B). After 12 and 24 months from baseline there is a reduction of 36.7% and 56.7% in class 1, of 42.1 and 56.6 in class 2, of 52 and 55.8% in class 3 respectively.

Pain VAS

507 patients affered to 00-04 group 1 of pain visual analogue scale (VAS) score, 1437 to 05-08 group 2 and 365 to 09-10 group 3. There is a statistically significant difference in the average NSAIDs consumption among pain VAS >8 group and the two others at baseline (Figure 2C).

After 12 and 24 months from baseline there is a reduction of 20.6% and 58.1% for the first, of 46.2% and 56.7% for the second, of 59.4% and 52.5% for third group.

Kellegren-Lawrence Radiological Classification

Patients affected by Kellegren-Lawrence (K/L) radiological grade 1 or 2, 3 and 4 were respectively 832, 762 and 246. There is no statistically significant difference in NSAIDs consumption in the three index groups (Figure 3A).

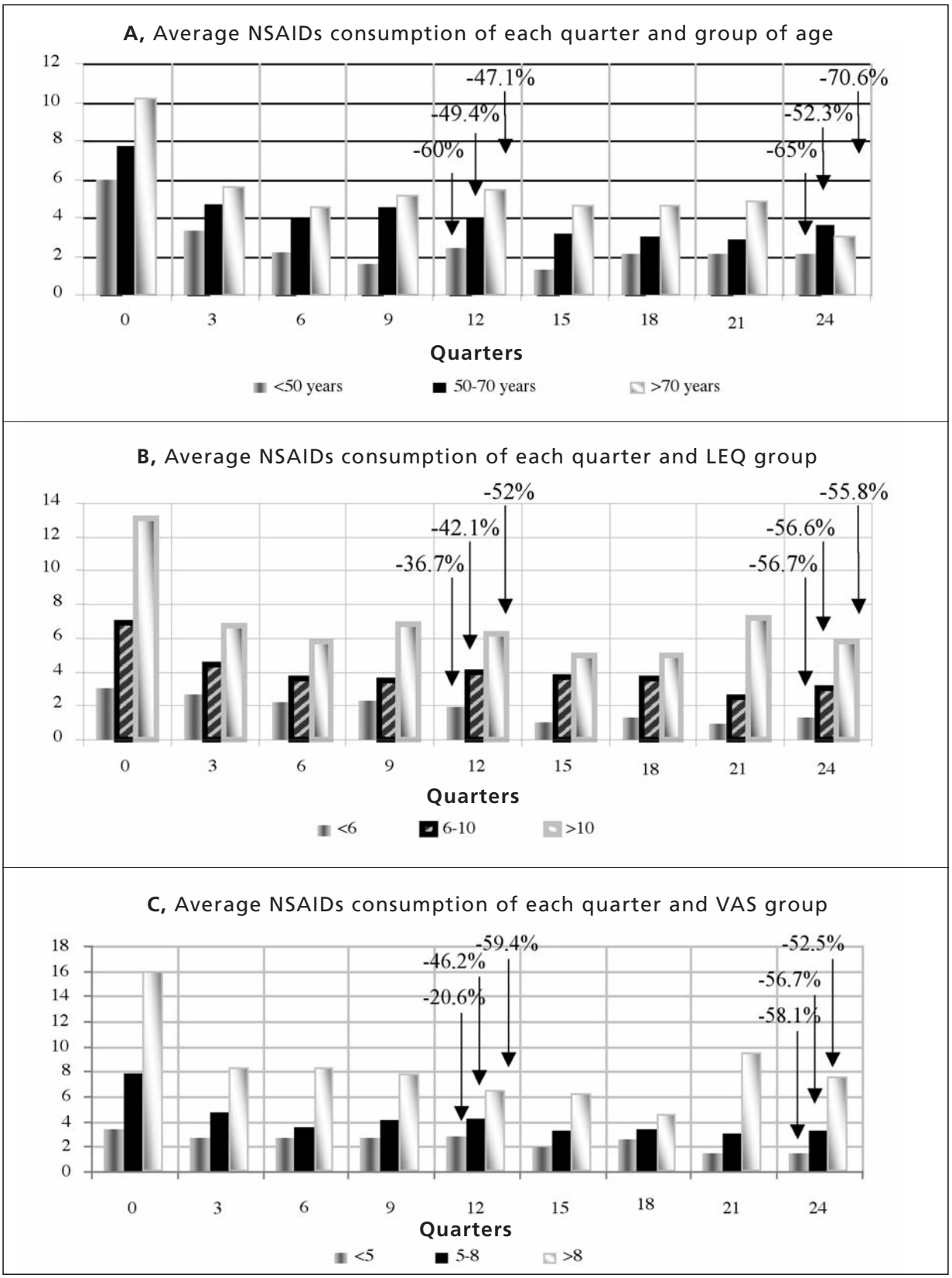
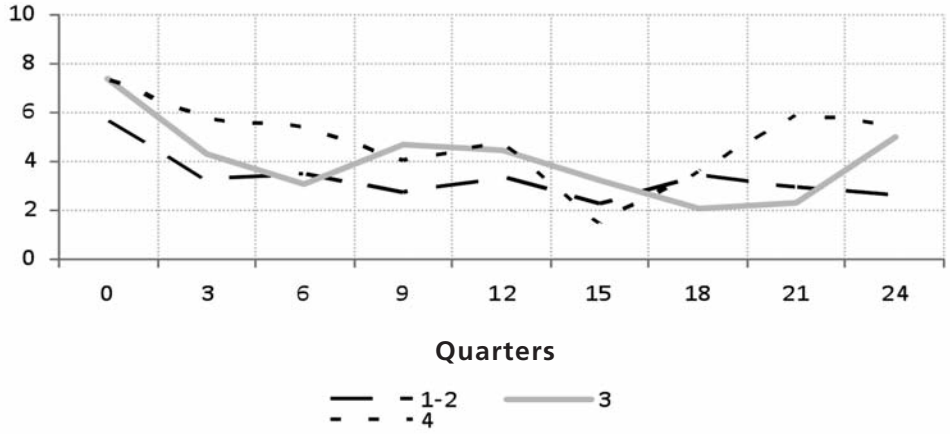
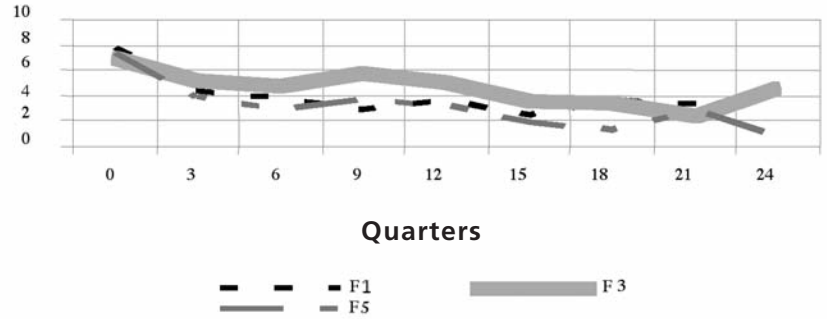


Figure 2. ***A,*** Average NSAIDs consumption of each quarter and group of age. ***B,*** Average NSAIDs consumption of each quarter and LEQ group. ***C,*** Average NSAIDs consumption of each quarter and VAS group.

A, Average NSAIDs consumption of each quarter and KI radiological classification



B, Average NSAIDs consumption of each quarter and drug



C, Mean NSAIDs consumption of rate for ultrasound pattern-based groups of patients

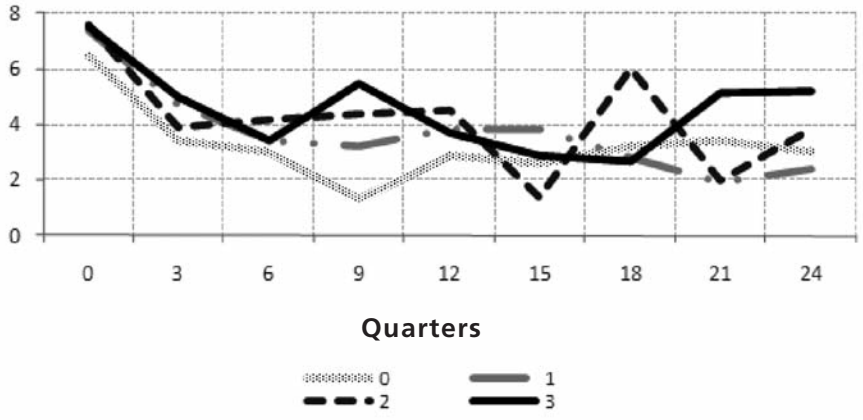


Figure 3. ***A,*** Average NSAIDs consumption of each quarter and radiological KL classification. ***B,*** Average NSAIDs consumption of each quarter and drug used. ***C,*** Average NSAIDs consumption of each quarter and ultrasound score.

HA used

Characteristics of three analized hyaluronic acid products are shown in Table II. A total of 878 patients were treated with Synvisc at the dose of 1 injection of one vial (2 ml) every six month. 503 patients were treated with Hyalubrix 60 mg at the dose of 1 injection of one vial (4 ml) every six month. 307 patients were treated with Jointex 32 mg at the dose of 1 injection of two vials (4 ml) every six month.

If the symptoms got worse each patient might be subject to an extra injection of the same product three months after precedent injection. There is no statistically significant difference in NSAIDs consumption among the three HA products examined over study time (Figure 3B).

Ultrasound Score

Patients presenting US score of 1, 2, 3 and 4 were respectively 329, 178, 203 and 338. There is no statistically significant difference in NSAIDs consumption among the four ultrasound score levels (Figure 3C).

Number of Injections

The total number of injections administered under ultrasound guidance during the 24-month study was 13,233 and patients received a mean of 5.6 injections. Figure 1 summarizes the number of patients per different injections numbers.

Discussion

This study is based on the "Italian national registry of hip ultrasound guided intrarticular treatment" data.

The registry was filled in with daily clinical experiences of physicians specialized in different medical fields such as Internal medicine, Radiology, Rheumatology, Physical medicine, Sports medicine. It reflects real life treatment data[20].

Our data, deduced from 2343 patients, suggest that hip ultrasound guided intra-articular treatment in symptomatic hip osteoarthritis may cause an important NSAIDs consumption reduction, measured as number of days during each month the patient takes NSAIDs to control pain. Our findings show that average NSAIDs consumption abruptly falls in the first three months comparing with percentage of the whole number which reaches a permanent level until 24 months. There were no significative differences in the average NSAIDs consumption comparing each quarter with the previous one ($p>0.05$). Anyway, NSAIDs consumption reduction is 50 and 61% at 12^{th} and 24^{th} month respectively. This result is obtained by the recurring treatment every at least six months, with the chance of one or two extra injections if needed. This approach allows therapy customization and the achievement of the lowest effective dosage. Actually every quarter following starting time the average NSAIDs consumption is significantly below than the baseline one ($p<0.0001$). These data get on well with our previous ones obtained by shorter as well as smaller studies[21-23]:

In VS of knee OA are similar data as well. In a systematic review Waddell[24] reported that cost effectiveness of intra-articular hyaluronans has been demonstrated and it can also be realised with reduction of NSAID medication use.

NSAIDs consumption reduction may entail clinical and social consequences. It is known that use of NSAIDs appear to be correlated with increased morbidity and mortality.

In 2009, Gislason et al[25] reported of 36,354 patients hospitalized with a primary congestive heart failure (CHF) diagnosis and discharged receiving a prescription for an NSAID. A total of 60,974 patients (56.9%) died during the course of the study.

NSAIDs were associated with a higher risk of mortality, ranging from a hazard ratio of 1.22 for naproxen to 2.08 for diclofenac. The increased risk in mortality appeared to be dose-dependent. There was also a consistent relationship between NSAID use and higher rates of subsequent death. On the contrary no death has been associated with VS of both hip and knee. HA products have been shown to have an excellent safety and efficacy profile as a viscosupplement for the OA of the knee and hip[17,21-23,26-28].

Moreover NSAIDs consumption reduction obtained by VS might decrease risk with an exponential model.

From an economical point of view NSAIDs consumption reduction implies not only decrease of direct costs but of indirect ones as well, related to PPI or misoprostol prescription for gastroprotection or to hospitalization for gastric or cardiovascular adverse events.

Considering hospitalization and co-prescribing costs in the UK, it has been estimated that the National Health Service spends on average £ 251 milion per year on NSAID induced GI side-effects[11]. A survey of the literature looking at these

costs throughout the world reveals similar scenarios elsewhere. It should be regarded as public health problem. In the UK there are about 12,000 emergency GI admissions per year attributable to NSAIDs[29].

Recent studies suggest that hospital admissions for congestive heart failure (CHF) are also increased appreciably in people taking NSAIDS. In a case-control study of patients admitted to hospital with their first episode of CHF, Henry et al[30] showed a relative risk of 2.3 (95% confidence interval 1.2 to 4.4) in users of non-steroidal anti-inflammatory drugs (defined as use in the previous 7 days). The burden of illness resulting from NSAID related congestive heart failure may exceed that resulting from gastrointestinal tract damage, approaching the same levels of morbidity and mortality. NSAIDs use increases with age[8] and the proportion of elderly patients taking NSAIDs has been estimated at as much as 25%[31]. Recently in a rewiev COX-2 selective NSAIDs were found to be similar to non-selective NSAIDs for the symptomatic relief of OA and to provide superior GI tolerability (the majority of evidence is in patients with OA). Although COX-2 selective NSAIDs offer protection against serious GI events, the amount of evidence for this protective effect varied considerably across individual drugs. The volume of trial evidence with regard to cardiovascular safety also varied substantially between COX-2 selective NSAIDs. Increased risk of MI compared to non-selective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient-years.

Conclusions

Intra-articular treatment with hyaluronic acid and its derivatives represents nowadays an important opportunity of hip osteoarthritis management. Many intra-articular hyaluronan formulations are available at this very moment differing each other in their physical properties, duration of effect and treatment schedules. Our findings point out not only that intra-articular hyaluronan preparations provide a reduction in NSAIDs consumption indicating hip OA pain relief. Since hip OA is a chronic disease multiple courses are required and this allows a better therapy customization for each patient a personalized management improving therapy effectiveness. NSAIDs consumption is strictly related to an high gastrointestinal and cardiovascular mortality and morbidity rate differently from HA intra-articular treatment that is well tolerated and is associated with a low incidence of adverse effects, usually localised to the injected joint. Local adverse events associated with intra-articular hyaluronan products are typically mild to moderate in severity, benign and transient.

The cost effectiveness of intra-articular hyaluronan has not been completely demonstrated because of the limited number of studies. Because different intra-articular hyaluronan formulations require different numbers of injections and office visits not all intra-articular hyaluronan formulations may be equally cost effective over time. The present study shows a reduction of NSAID intake in a large cohort of patients for a long period of followup after hip viscosupplementation. We suggest further study of cost-effectiveness and cost-utility as in knee OA[32].

Acknowledgements

The study was conducted with unrestricted funds from "National Foundation for Hip intra-articular Treatment with Ultrasound Guidance" (ANTIAGE Onlus), Rome, Italy.

Special thanks go to our co-workers, Dr L.S. Martin Martin, Dr A. Ragno, Dr A. Raco, Dr F. Vacca Dr F. Giovannangeli and, for data collection, Mr V. Pileggi, Mr R. Taschini and Mr M. Mei.

We thank also the following members of ANTIAGE Foundation: Dr Altomonte L. (Roma), Dr D'Avola G. (Catania), Dr Massarotti M. (Milano), Dr Zaccari G. (Roma), Dr Baldi (Civitavecchia), Dr Ranieri M. (Tagliacozzo).

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